Solvants

Utilisation en masse dans la production de produits chimiques fins

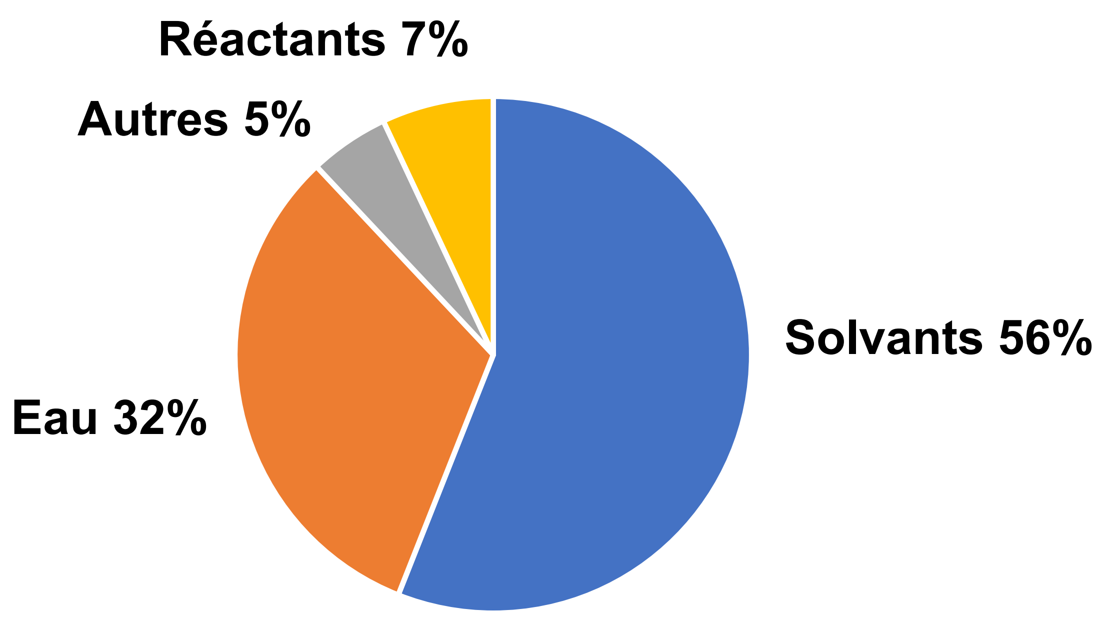
- *Principe #1 : Prévention des déchets*

- *Utilisations de solvants :*

1. *milieux réactionnels chimiques*
2. *séparation et purification*
3. *technologies de nettoyage*

- *Solvants organiques :*

1. Bon support pour le transfert de chaleur et de masse
2. Faible viscosité (cinétique de réaction plus élevée)



Composition en masse des types de matériaux utilisés pour la fabrication de API (Ingrédient Pharmaceutique Actif) : les solvants représentent 50 % des matériaux utilisés !

Solvants

- Pourquoi utiliser un solvant ?
- Réactions sans solvant
- Eau
- Liquides ioniques
- CO_2 supercritique
- Solvants fluorés

"Practical Approaches to Green Solvents"
DeSimone, J. M., *Science* **2002**, *297*, 799–803

"Green Solvents for Sustainable Organic Synthesis: State of the Art"
Sheldon, R. A. *Green Chem.* **2004**, *7*, 267–278

"A Green Chemistry Approach to Asymmetric Catalysis: Solvent-free and Highly Concentrated Reactions"
Walsh, P. J.; Li, H.; de Parrodi, C. A. *Chem. Rev.* **2007**, 107, 2503–2545

Solvent selection guides

- *Prominent Solvent Selection Guides*

Pfizer:

The first company to publish a color-coded guide
"preferred", "usable", or "undesirable"

Alfonsi, K. *et* al. *Green Chem.* **2008**, *10*, 31.

GSK (GlaxoSmithKline):

Involves a detailed breakdown of scores of different EHS categories
"few issues", "some issues", or "major issues"

Henderson, R. K. *et al. Green Chem.* **2011**, *13*, 854.

Sanofi:

Most recent guide featuring more solvents
"recommended", "substitution advisable", or "substitution requested"

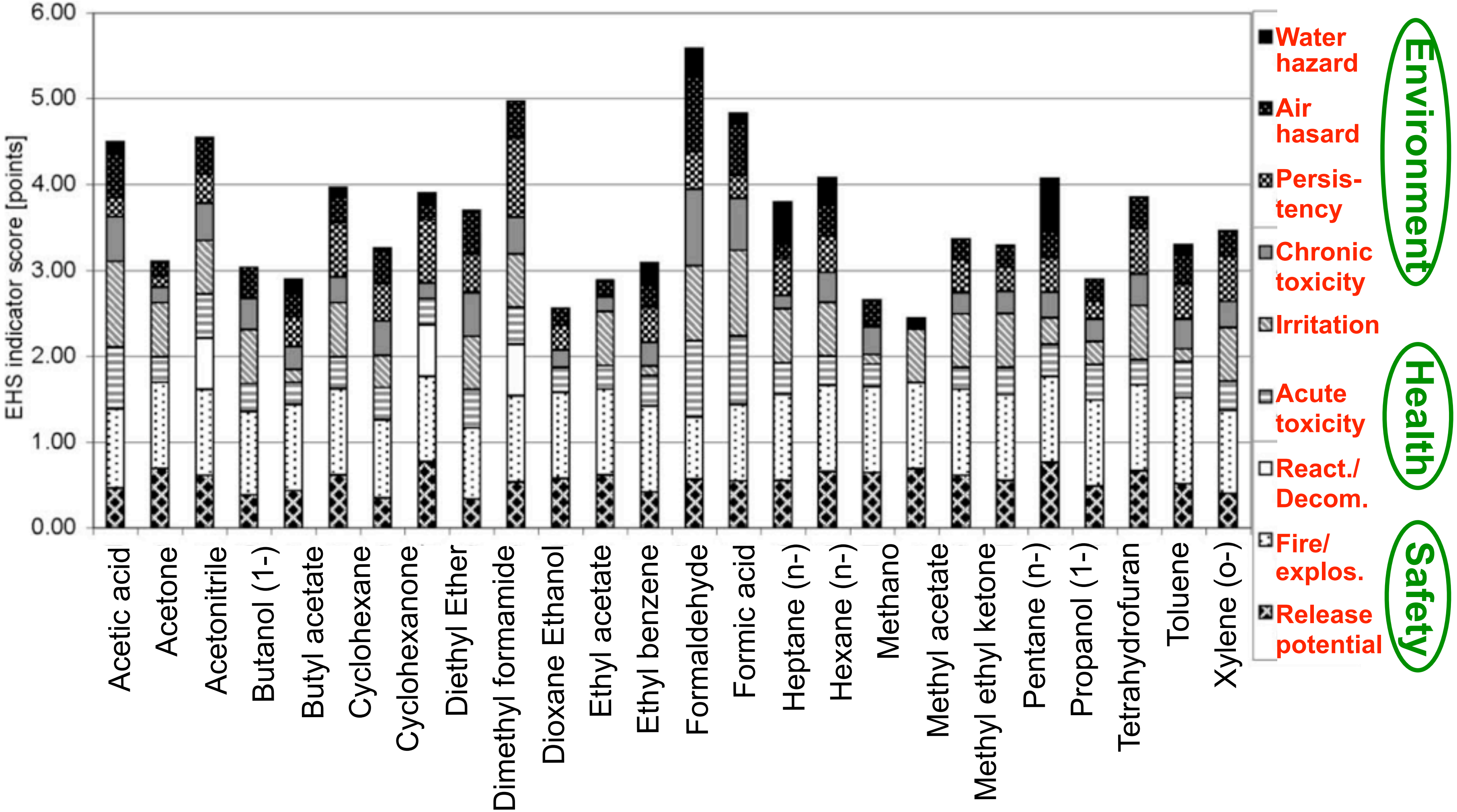
Prat, D. *et al. Org. Process Res. Dev.* **2013**, *12*, 1517.

Solvents

Solvent	Pfizer	GSK	Sanofi	Overall
Water	Preferred	Few issues	Recommended	Recommended
Ethanol	Preferred	Few issues	Recommended	Recommended
Ethyl acetate	Preferred	Few issues	Recommended	Recommended
Me-THF	Usable	Some issues	Recommended	Problematic
Acetonitrile	Usable	Some issues	Recommended	Problematic
CH_2Cl_2	Undesirable	Major issues	Substitution advisable	Hazardous
Hexane	Undesirable	Major issues	Substitution requested	Hazardous
DMF	Undesirable	Major issues	Substitution requested	Hazardous

Solvants

- Évaluation “EHS” des solvants organiques



“What is a green solvent? A comprehensive framework for the environmental assessment of solvents”
Capello, C.; Fischer, U.; Hungerbühler, K. *Green Chem.* **2007**, *9*, 927–934

Solvants

Guide sélection GSK

- *Analyse détaillée des scores des différentes catégories EHS*
- *Solvants verts disponibles dans différentes classes de solvants*
  - *Acide acétique (qqs problèmes), eau*
  - *Alcools : méthanol (qqs problèmes), éthanol, éthylène glycol, …*
  - *Esters : acétate d'éthyle, glycérol diacétate, …*
  - *Carbonates : diméthyl carbonate (DMC), diéthyl carbonate (DEC), propylène carbonate*
  - *Cétones : acétone (qqs problèmes), méthyl isobutyl cétone*
  - *Aromatiques : anisole*

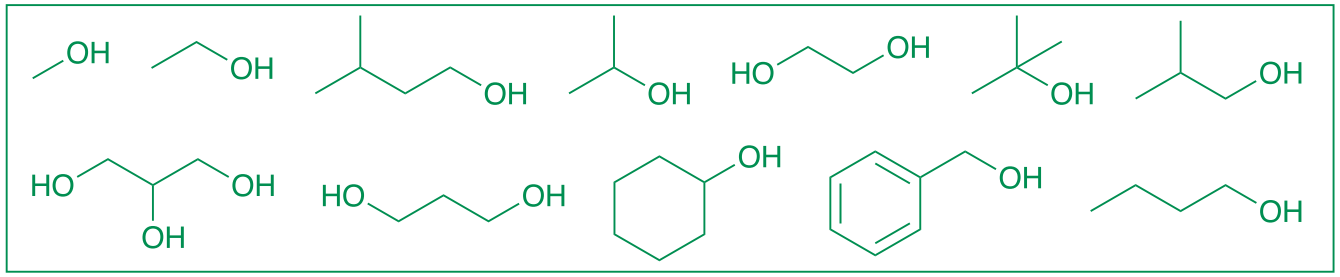
  - *Alcanes : cyclohexane (qqs problèmes), heptane (qqs problèmes)*
  - *Éthers : 2-Me-THF (qqs problèmes), cyclopentyl méthyl éther (qqs problèmes)*
  - *Aprotiques polaires : MeCN (qqs problèmes), DMSO (qqs problèmes)*
  - *Solvants chlorés : –*
- *Catégories où il manque des solvants de remplacement :*
  - *Alcanes*
  - *Éthers : important (pour remplacer : Et_2O, THF)*
  - *Polaires aprotiques : important (pour remplacer : DMF, DMAC, NMP)*
  - *Solvants chlorés*

Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla; Shuster, L. E.; Sneddon, H. F. *Green Chem.* **2016**, *18*, 3879. Henderson, R. K. *et al. Green Chem.* **2011**, *13*, 854.

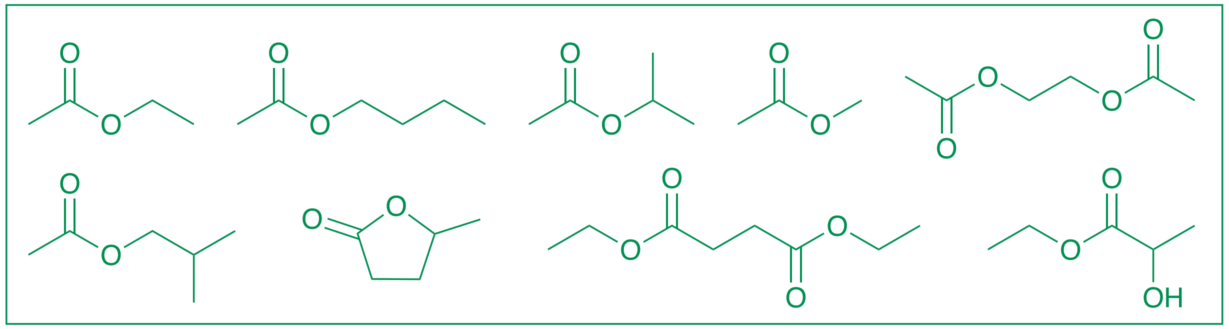
Solvants

- *Solvants verts disponibles dans différentes classes de solvants*

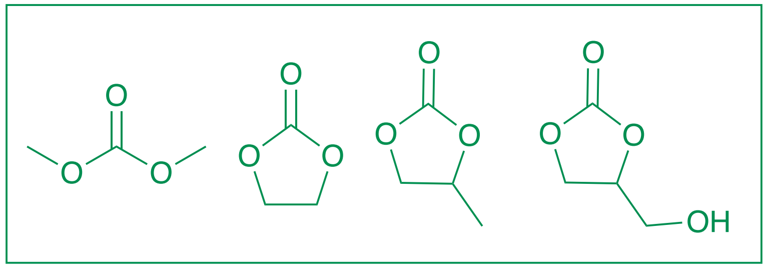
  - *Acide acétique (qqs problèmes), eau*
  - *Alcools : méthanol (qqs problèmes), éthanol, éthylène glycol, …*



  - *Esters : acétate d'éthyle, glycérol diacétate, …*



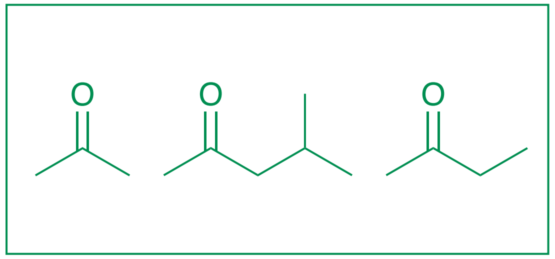
  - *Carbonates : diméthyl carbonate (DMC), diéthyl carbonate (DEC), propylène carbonate*



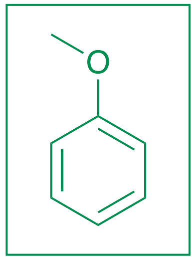
Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla; Shuster, L. E.; Sneddon, H. F. *Green Chem.* **2016**, *18*, 3879. Henderson, R. K. *et al. Green Chem.* **2011**, *13*, 854.

Solvants

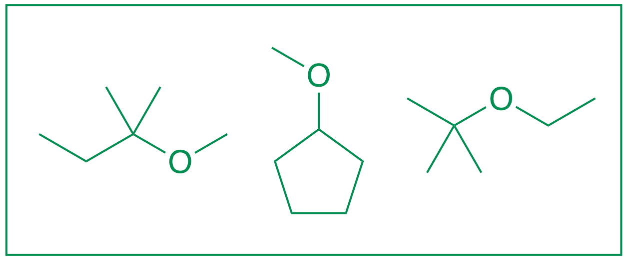
- *Solvants verts disponibles dans différentes classes de solvants*
  - *Cétones : acétone (qqs problèmes), méthyl isobutyl cétone*



  - *Aromatiques : anisole*



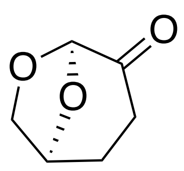
  - *Éthers : 2-Me-THF (qqs problèmes), cyclopentyl méthyl éther (qqs problèmes)*



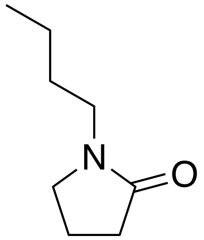
Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla; Shuster, L. E.; Sneddon, H. F. *Green Chem.* **2016**, *18*, 3879. Henderson, R. K. *et al. Green Chem.* **2011**, *13*, 854.

Solvants

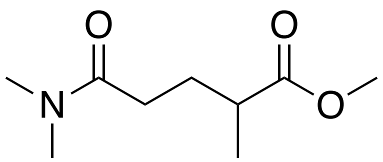
- *Solvants de substitution dans la classe des solvants aprotiques polaires*
  - *Alcanes*
  - *Éthers : important (pour remplacer : Et_2O, THF)*
  - *Aprotiques polaires : important (pour remplacer : DMF, DMAC, NMP, …)*
  - *Solvants chlorés*



Cyrène



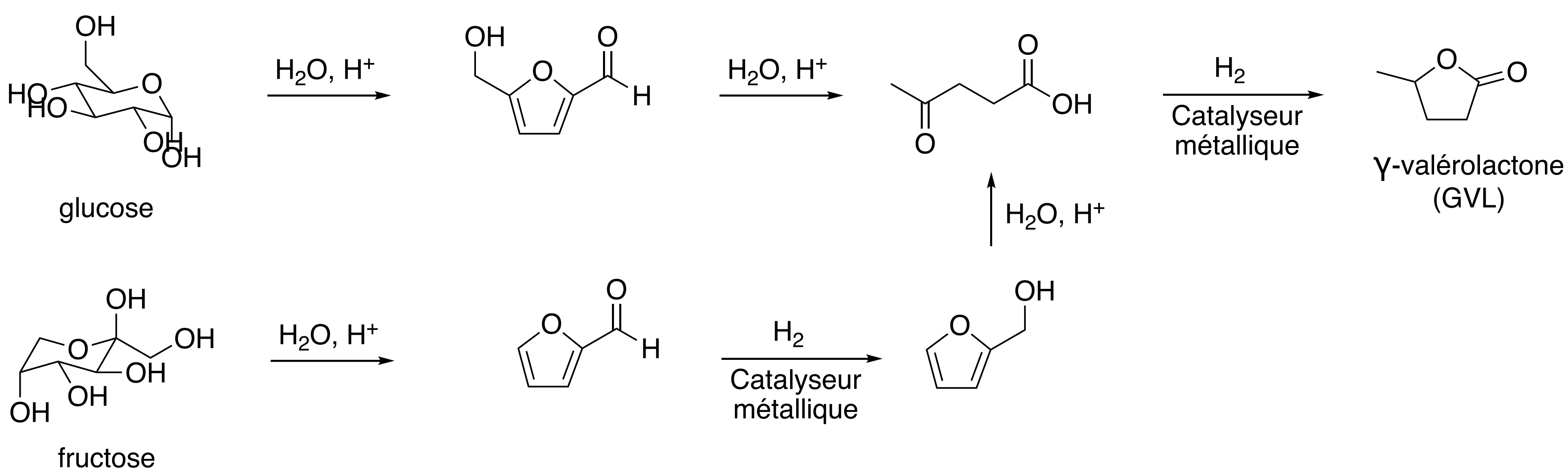
NBP



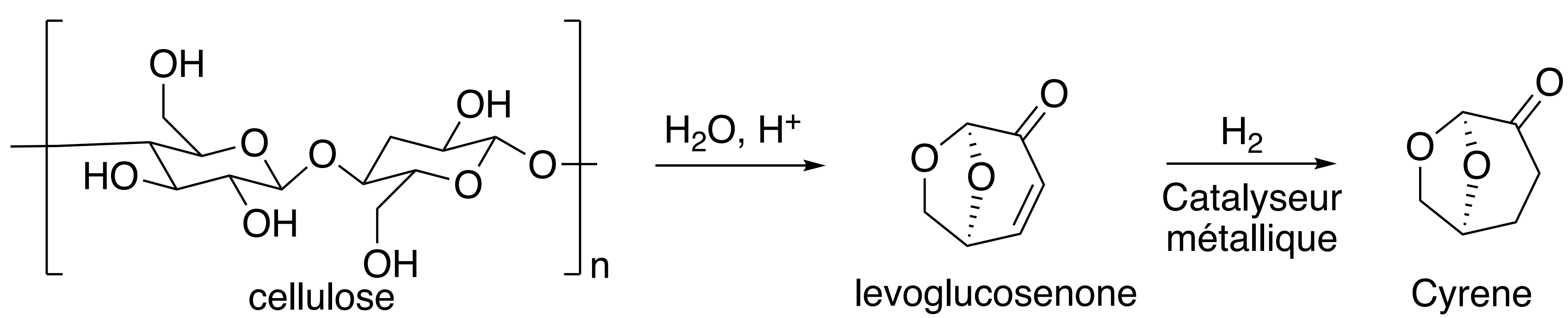
PolarClean (Solvay)

Solvants fabriqués à partir de cellulose

- *Gamma-valérolactone (GVL)*



- *Dihydrolévoglucosénon (Cyrène)*



Clark, J. H. *et al. Chem. Commun.* **2014**, *50*, 9650

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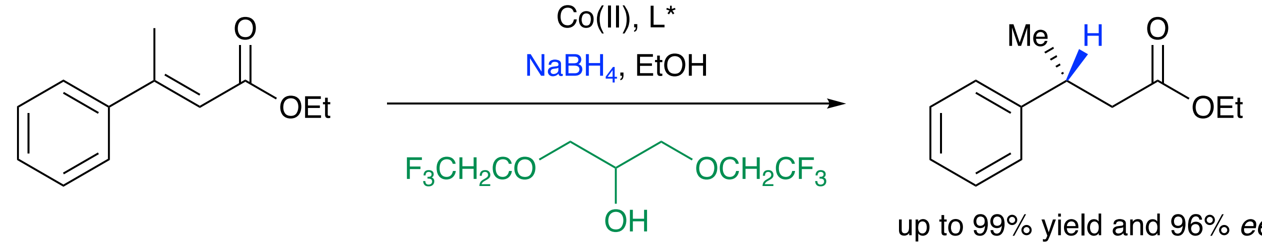
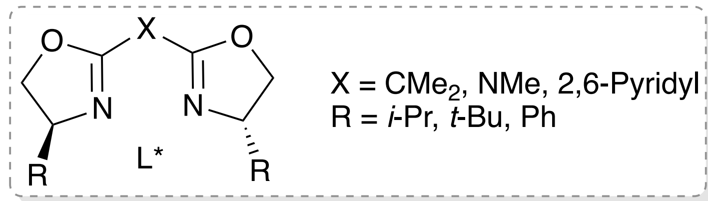
Exemples de réaction dans des solvants de type alcool/glycérol

- *Réaction de réduction (1) – Réaction de réduction (2)*

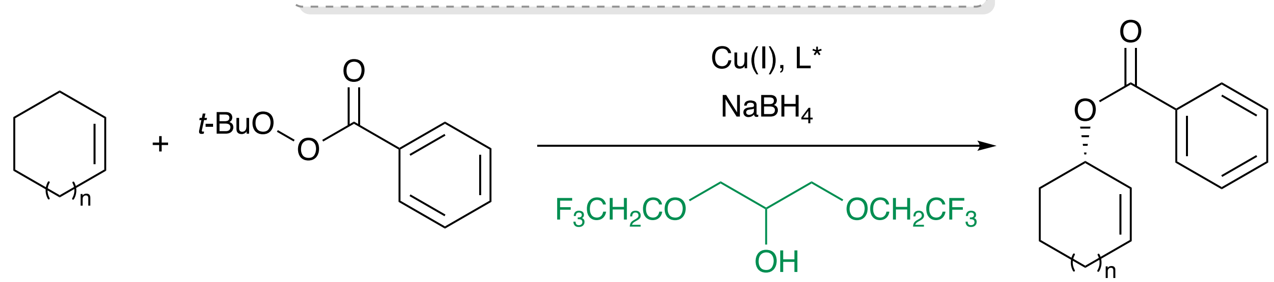
(1)



up to 99% yield and 96% *ee*

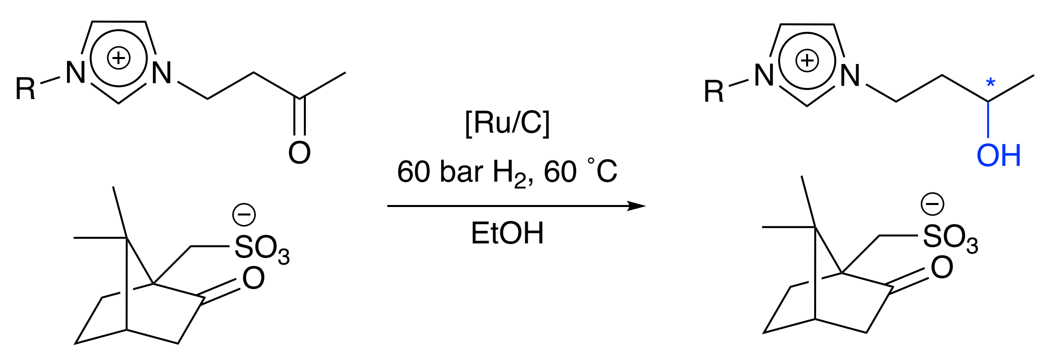


(2)



up to 85% *ee*

- *Réaction de réduction de cétone*



Up to 94% *ee*

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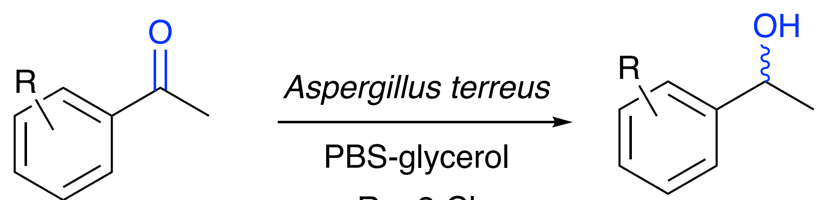
Exemples de réaction dans des solvants de type alcool/glycérol

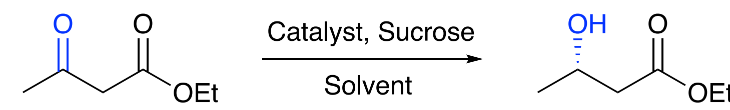
- *Réaction de réduction de cétone*



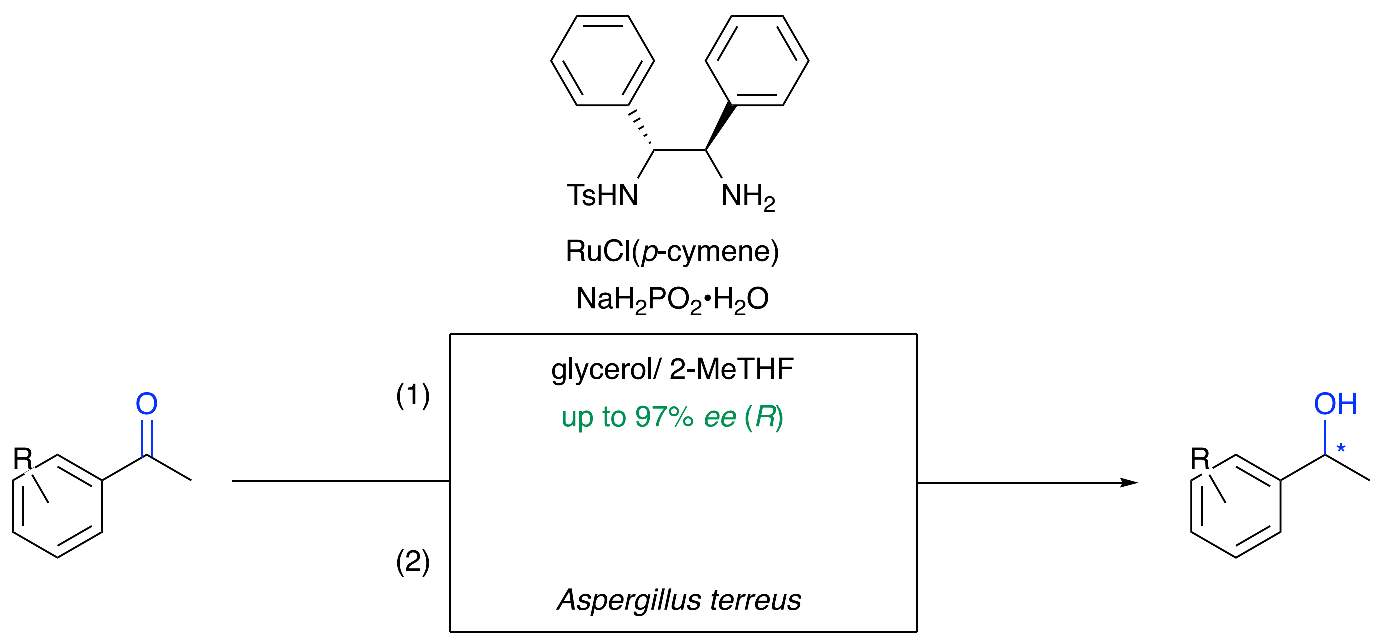
R = 2-Cl

PBS: glycerol = 9: 1, (*S*) 92% *ee*

PBS: glycerol = 4: 1, (*S*) >99% *ee*



Entry	Catalyst	Solvent	Conversion (%)	*ee* (%)
1	Free BY	Glycerol	74	>99
2	Imm. BY	Glycerol	99	>99
3		Water	100	99
4		Ionic liquid	70	95
5		Fluorous phase	100	95



PBS-glycerol

R = 2-Cl

PBS: glycerol = 9: 1, (*S*) 92% *ee*

PBS: glycerol = 4: 1, (*S*) >99% *ee*

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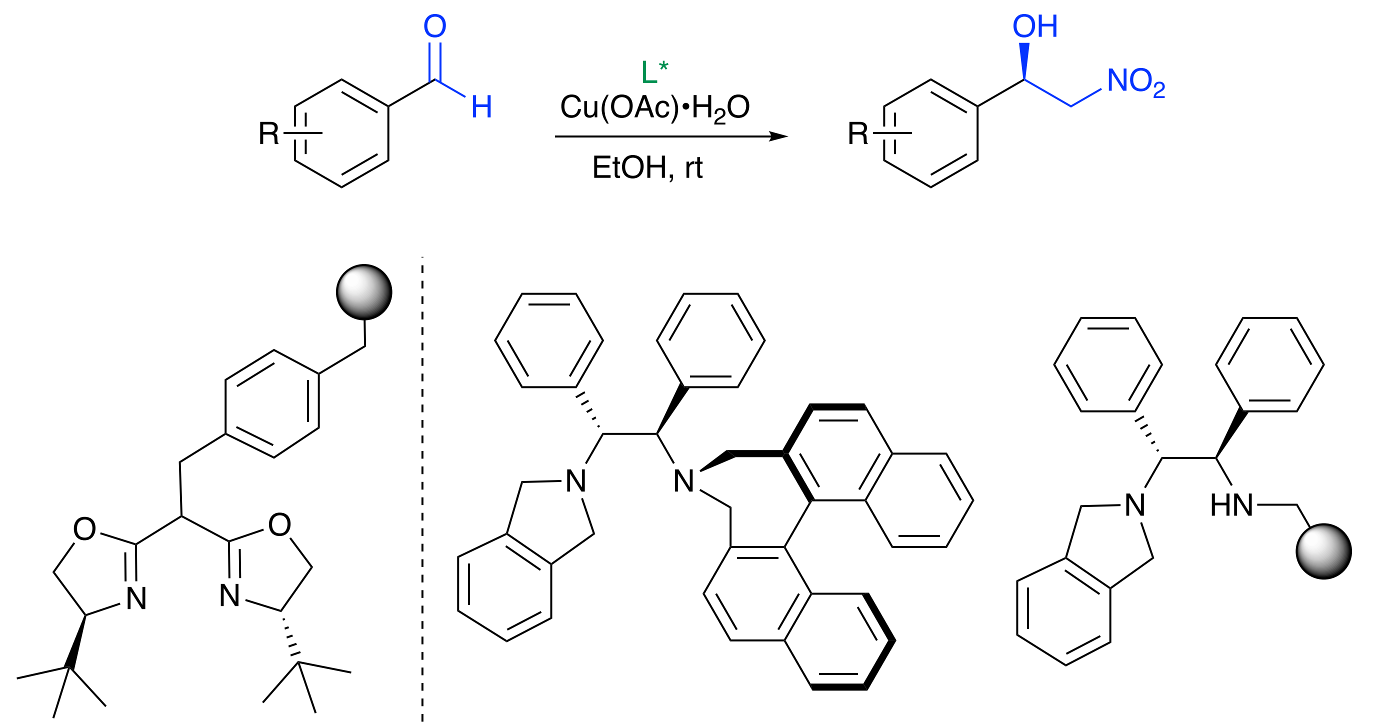
Exemples de réaction dans des solvants de type alcool/glycérol

- *Réaction de Henry*



L1
Up to 97% yield, 88% *ee*

L2
Up to >99% yield, 98% *ee*

L3
Up to >99% yield, 96% *ee*

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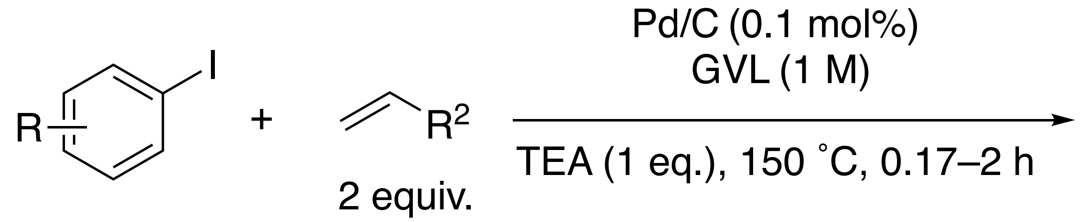
Exemples de réaction dans des solvants de substitution (apolaires aprotiques)

- *Réaction de Heck*

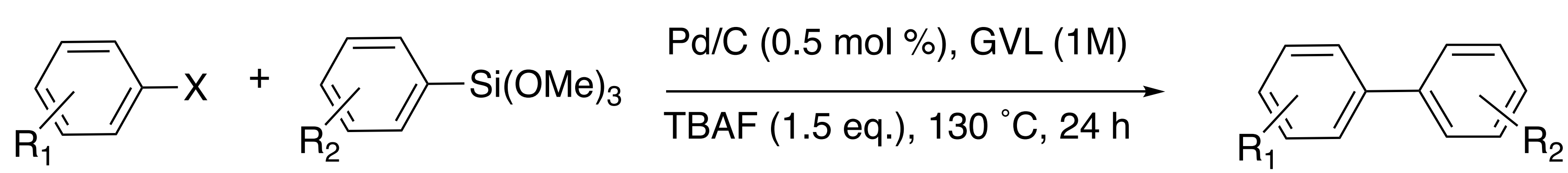


R^2 = aryl, CO_2R

82–90 %

GVL

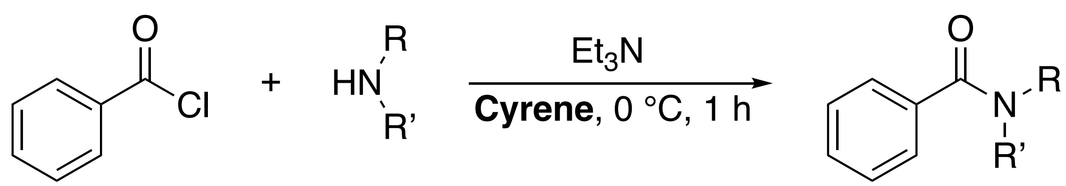
- *Réaction de Hiyama*



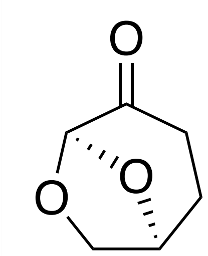
Strappaveccia, G.; Ismalaj, E.; Petrucci, C.; Lanari, D.; Marrocchi, A.; Drees, M.; Facchetti, A.; Vaccaro, L., *Green Chem.* **2015,** *17*, 365
Ismalaj, E.; Strappaveccia, G.; Ballerini, E.; Elisei, F.; Piermatti, O.; Gelman, D.; Vaccaro, L. *ACS Sustainable Chem. Eng.* **2014**, *2*, 2461

Cyrène

- *Synthèse d'amides*

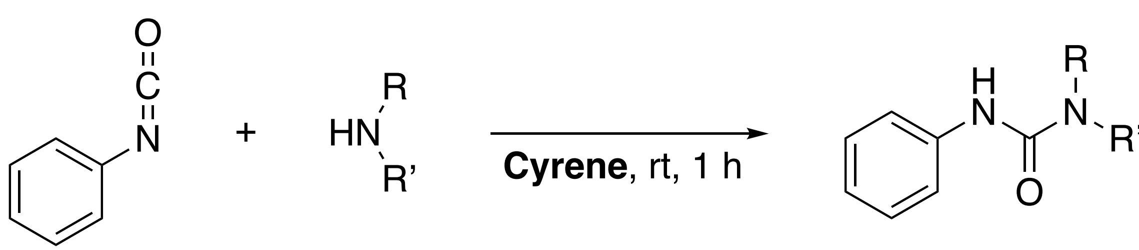


Up to 91%
No column chromatography



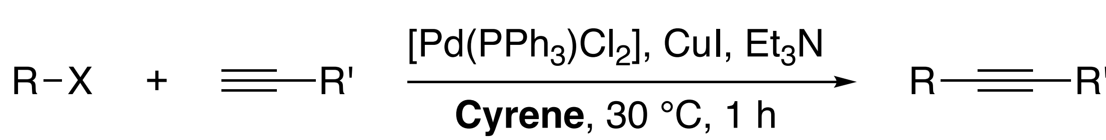
Cyrène

- *Synthèse d'urées*

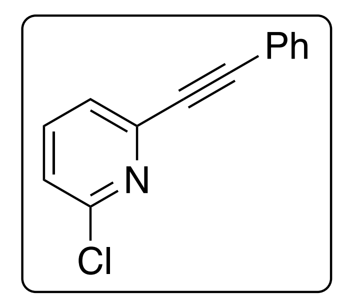


46–99%
No column chromatography

- *Réaction de couplage de Sonogashira*



60–100%



Green Chem. **2019**, *21*, 3675–3681
Green Chem. **2017**, *19*, 2123–2128
Beilstein J. Org. Chem. **2016**, *12*, 2005–2011

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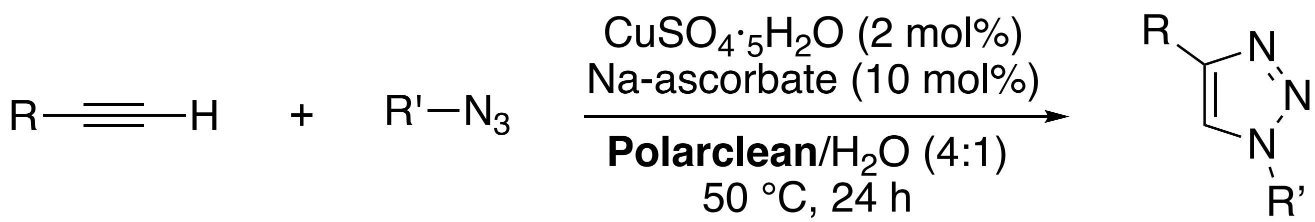
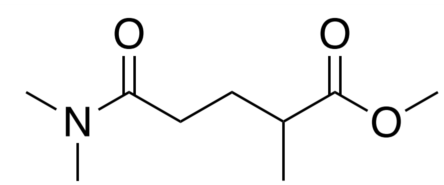
PolarClean

- *Réaction click*

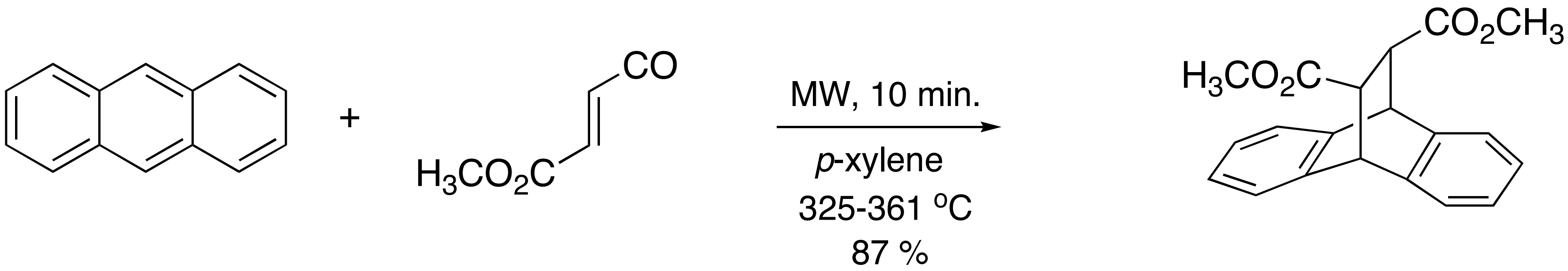


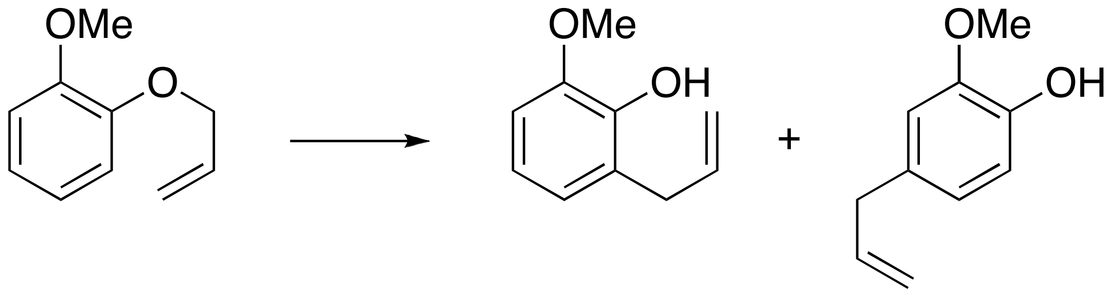


PolarClean
(Solvay)

- *Excellents rendements*
- *E-factor très bas (réaction click) : 2.6–3.7*
- *Pas de colonne de chromatographie*
- *Catalyseur et solvants peuvent être recyclés.*

Réactions sans solvant

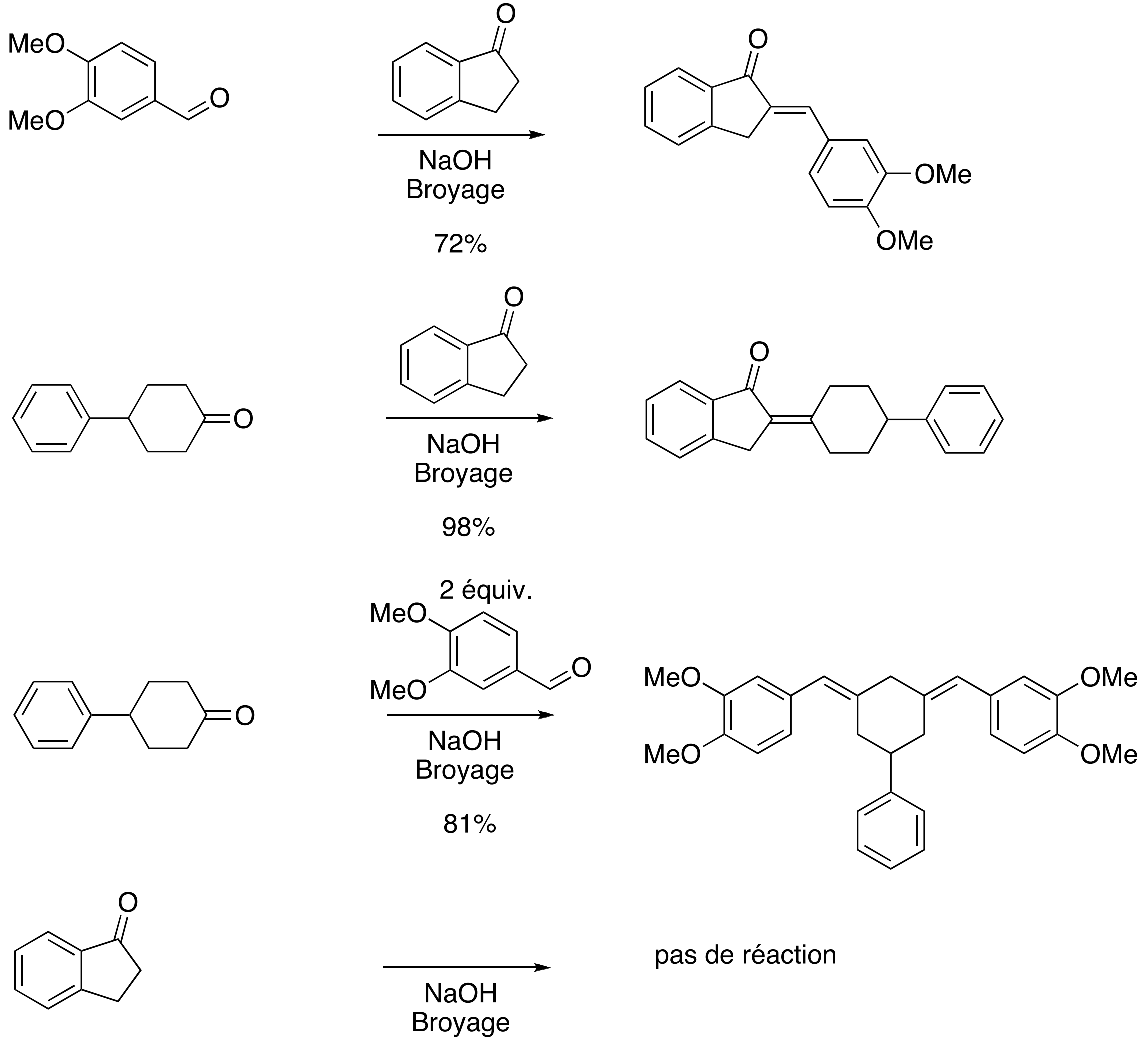




5 min., DMF, 300-315 °C, micro-ondes, 72 %
90 sec. HCONHMe, 276-300 °C, micro-ondes, 87 %
12 min., “neat” (pur), 370-400 °C, micro-ondes, 71 %

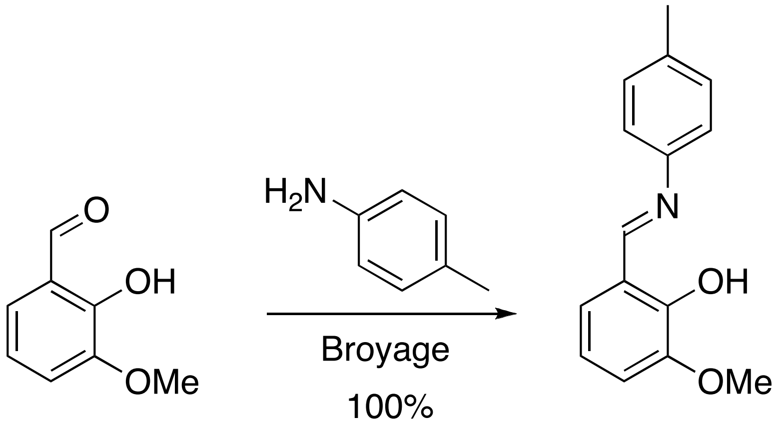
“Application of commercial microwave ovens to organic synthesis”
Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G., *Tetrahedron Lett.* **1986**, *27*, 4945–4948

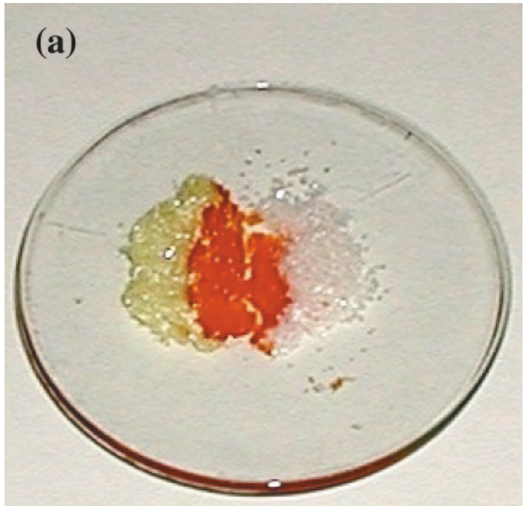
Réactions sans solvant

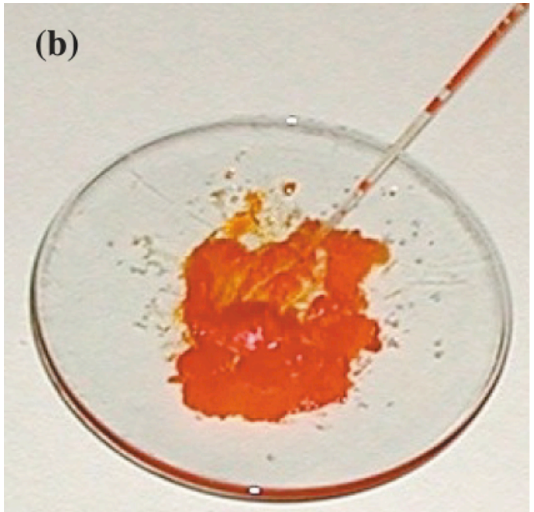


“Recent Advances in Solventless Organic Reactions: Towards Benign Synthesis with Remarkable Selectivity”
Cave, G. W. V.; Raston, C. L.; Scotta, J. L., *Chem. Commun.* **2001**, 2159–2169

Réactions sans solvant

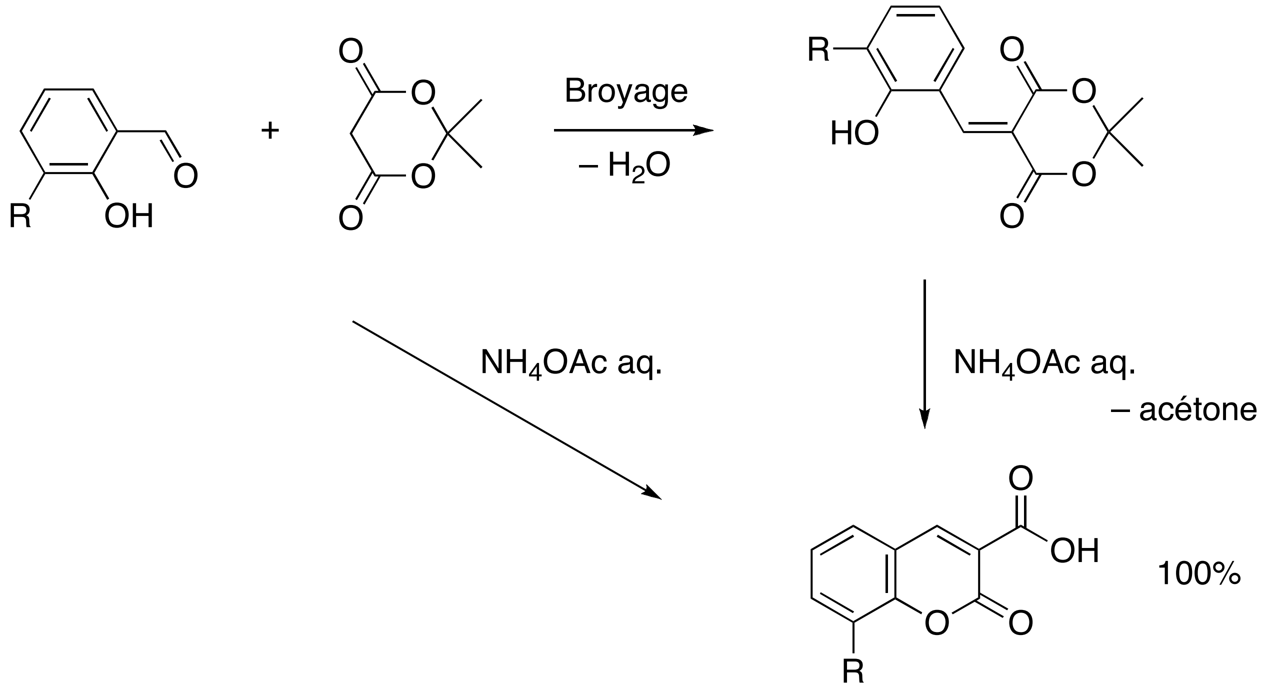






"Recent Advances in Solventless Organic Reactions: Towards Benign Synthesis with Remarkable Selectivity"
Cave, G. W. V.; Raston, C. L.; Scotta, J. L., *Chem. Commun.* **2001**, 2159–2169
"Quantitative solid–solid synthesis of azomethines"
Schmeyers, J.; Toda, F.; Boy, J.; Kaupp, G., *J. Chem. Soc., Perkin Trans. 2*, **1998**, 989–993

Réactions sans solvant

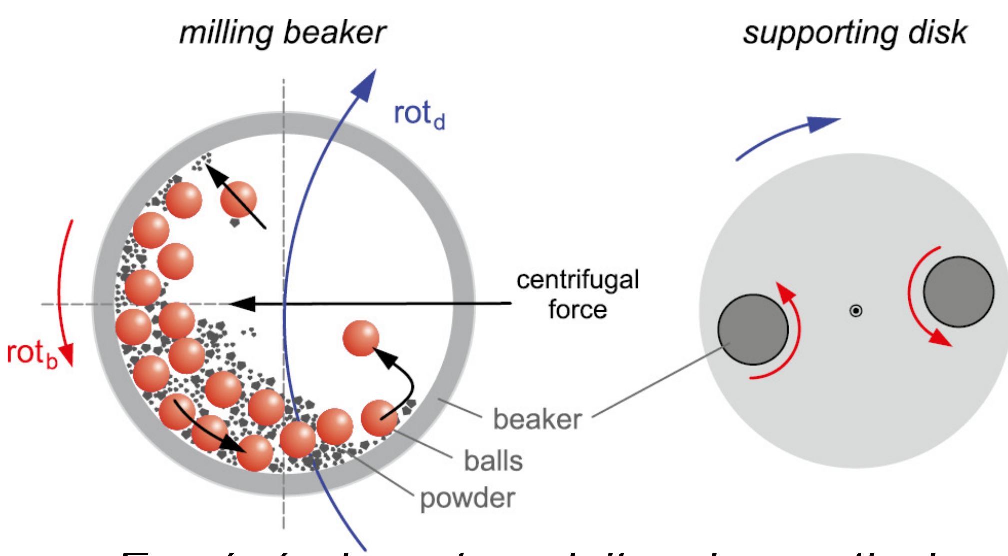


"Recent Advances in Solventless Organic Reactions: Towards Benign Synthesis with Remarkable Selectivity"
Cave, G. W. V.; Raston, C. L.; Scotta, J. L., *Chem. Commun.* **2001**, 2159–2169

Mécanochimie

Principes

- *Autre terme « mécanosynthèse »*
- *Approche sans solvant*
- *Solution d'intérêt (économie d'atomes et de solvants, chimie verte)*
- *Processus à l'état solide : transformations chimiques induites par des forces mécaniques : sous la forme de cisaillement, de compression et de friction*
- *Appareillage : « ball-mill », « grinding » (broyage)*



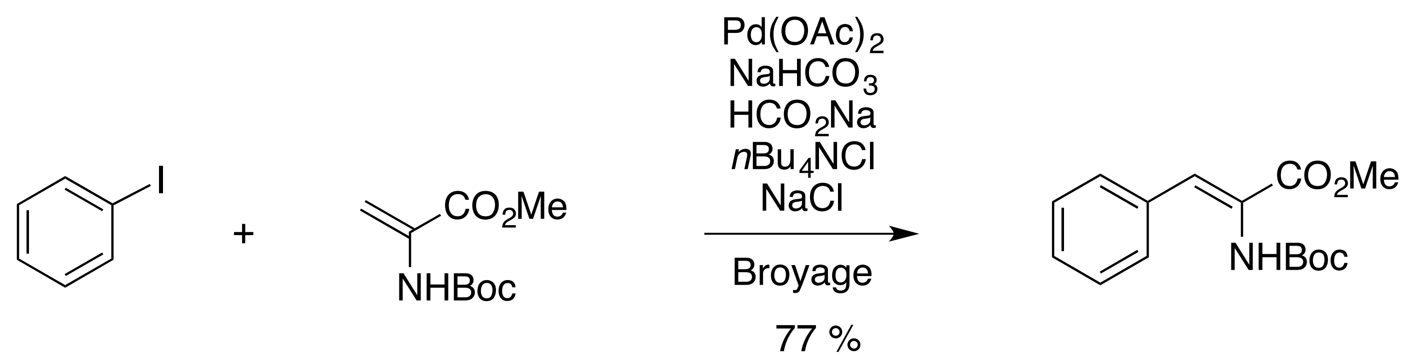
- *En général, sont produites des particules de < 100 nm*
- *Technique parallèle : broyage assisté par un liquide (concentrations très élevées)*

Bolm 2008GC1131

Mécanochimie

Exemples

- *Réaction de Heck*



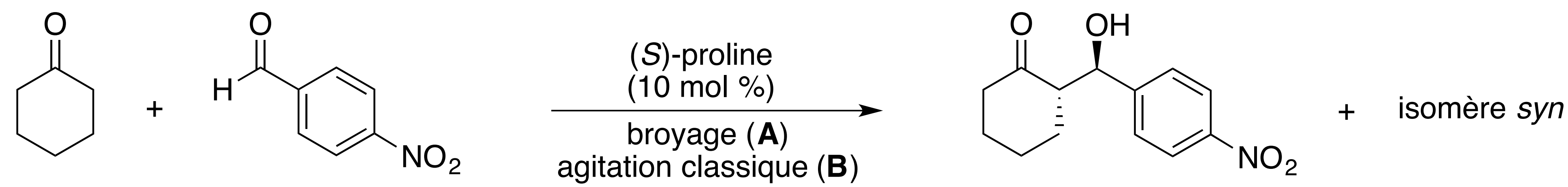
80 °C, 1 h, sans broyage : 18–33 %

Frejd 2004JOM3778

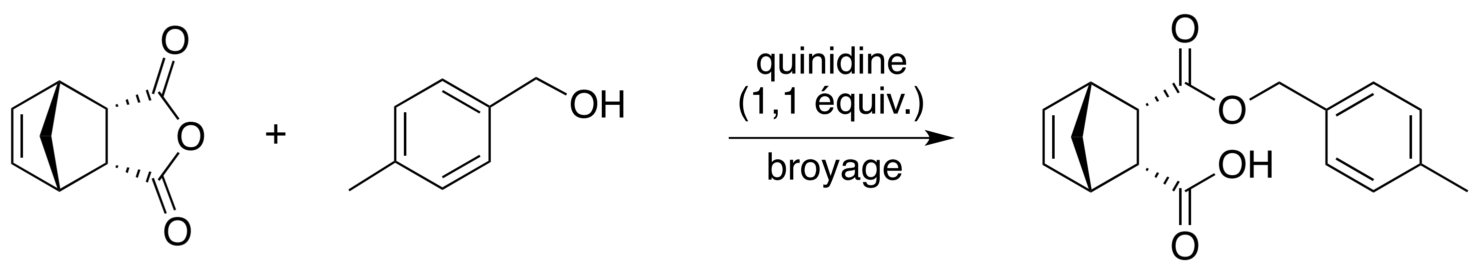
Mécanochimie

Exemples en synthèse stéréosélective

- *Temps de réaction beaucoup plus courts*



A	5,5 h	99 %	*ee* 94 %	*anti*/*syn* 89:11
B	96 h	98 %	*ee* 94 %	*anti*/*syn* 87:13

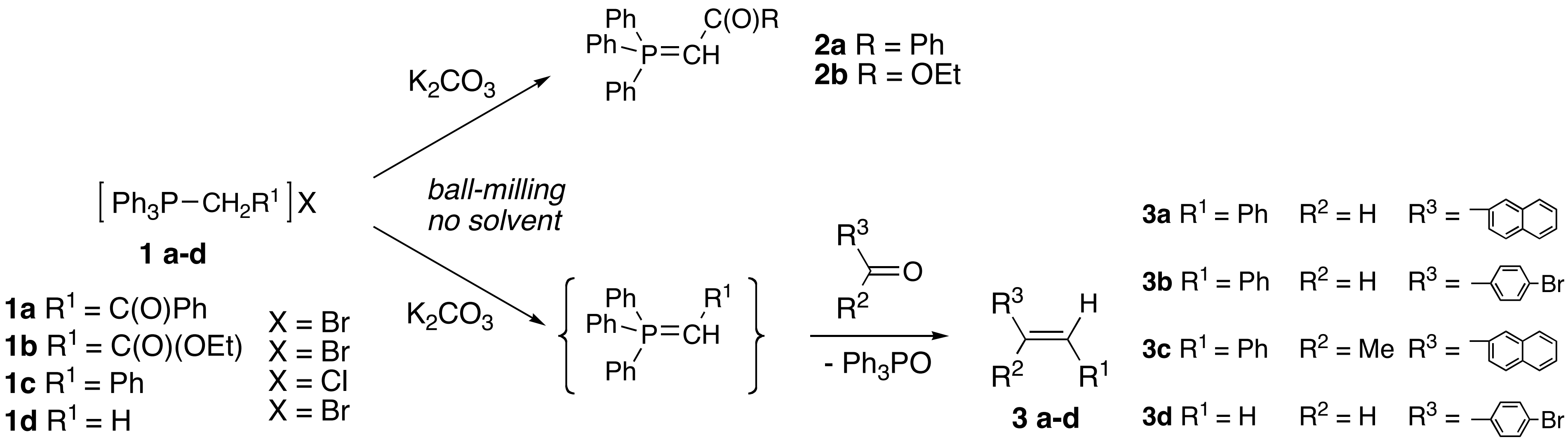


1,1 équiv. 91 % *ee* 61 %

- *Conditions classiques avec solvant : PhMe, – 60 °C, 24–48 h, 99 %*
- *Énantiosélectivité se compare avec celle obtenue en conditions classiques (60 °C)*
- *1,1 équiv. alcool benzylique au lieu de 3 équiv., pas de work-up*

Bolm 2006ACIE6924

Réactions sans solvant



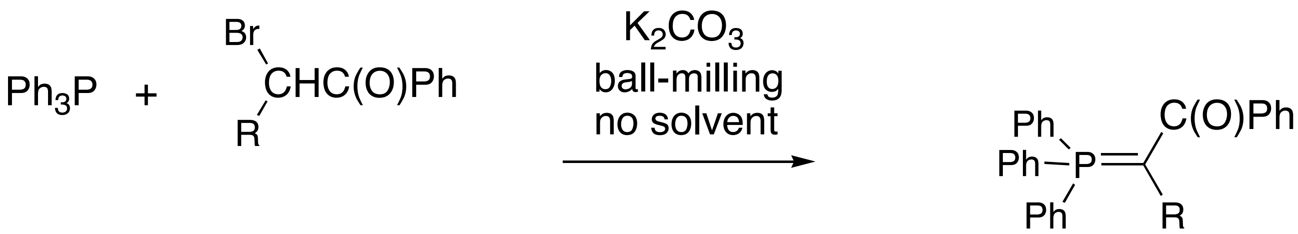
Mechanochemically Prepared Compounds

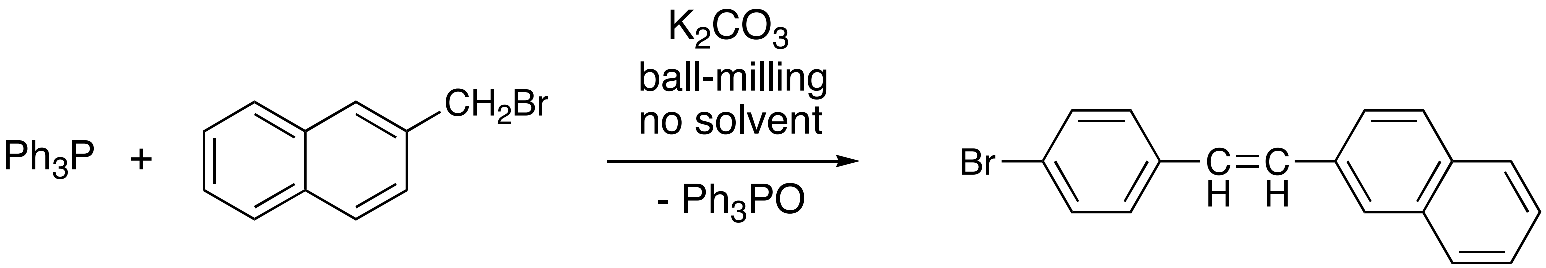
compound	miling time, h	yield, %	E:Z ratio	reference
2a	3	99	-	*c*
2b	4	96	-	3b, 8
3a	7	85	1.6 : 1	7
3b	8	92	2 : 1	9
3c	14	70	3.4 : 1	10
3d	20	73	-	11
4	4	99	-	6
5	8	93	3.5 : 1	7

“Mechanically Induced Solid-State Generation of Phosphorus Ylides and the Solvent-free Wittig Reaction” Balema, V. P.; Wiench, J. W.; Pruski, M.; Pecharsky, V. K., *J. Am. Chem. Soc.* **2002**, 124, 6244–6245

Réactions sans solvant

- Wittig “one-pot” par mécanochimie :



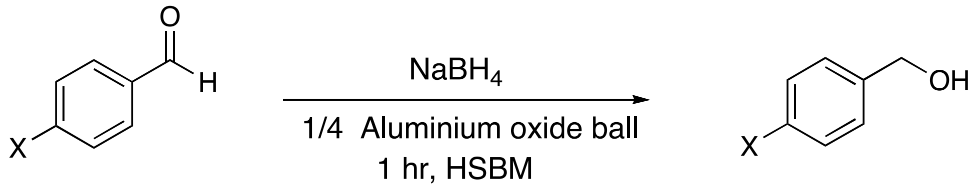


“Mechanically Induced Solid-State Generation of Phosphorus Ylides and the Solvent-free Wittig Reaction” Balema, V. P.; Wiench, J. W.; Pruski, M.; Pecharsky, V. K., *J. Am. Chem. Soc.* **2002**, 124, 6244–6245

Réactions sans solvant

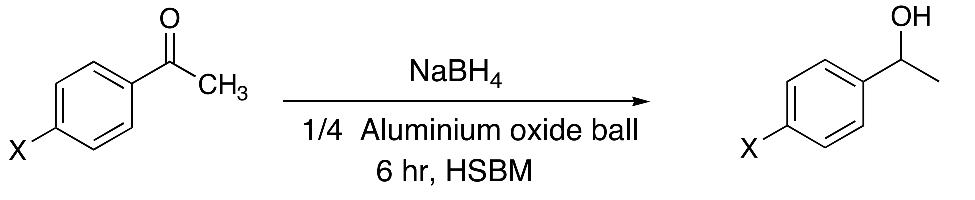
- Mécanochimie via une “bille à haute vitesse” :

Reduction of *p*-substituted aryl aldehydes by HSBM



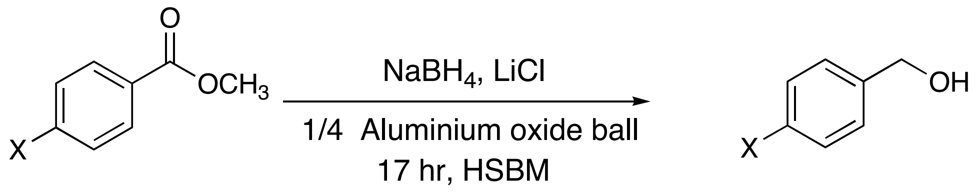
X = Br, H, NO_2, OMe

Reduction of *p*-substituted aryl ketones by HSBM



X = Br, H, NO_2, OMe

Solvent-free reduction of ester by HSBM



X = Br, H, NO_2, OMe

Although most of the research conducted in this area has been performed by using a mortar and pestle, high speed ball-milling (HSBM) is an attractive solvent-free method that has started to gain attention. In the HSBM method, a ball bearing is placed inside a vessel that is shaken at high speeds. The high speed attained by the ball-bearing has enouhg force to make an amorphous mixture of the reagents which subsenquently facilitates a chemical reaction.

“The first solvent-free method for the reduction of esters”
Mack, J.; Fulmer, D.; Stofel, S.; Santos, N., *Green Chem.* **2007**, *9*, 1041–1043